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THE EPIDEMIOLOGY OF VANCOMYCIN-RESISTANT *ENTEROCOCCUS* COLONIZATION IN A MEDICAL INTENSIVE CARE UNIT

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ABSTRACT

OBJECTIVE: To determine the epidemiology of colonization with vancomycin-resistant *Enterococcus* (VRE) among intensive care unit (ICU) patients.

DESIGN: Ten-month prospective cohort study.

SETTING: A 19-bed medical ICU of a 1,440-bed teaching hospital.

METHODS: Patients admitted to the ICU had rectal swab cultures for VRE on admission and weekly thereafter. VRE-positive patients were cared for using contact precautions. Clinical data, including microbiology reports, were collected prospectively during the ICU stay.

RESULTS: Of 519 patients who had admission stool cultures, 127 (25%) had cultures that were positive for VRE. Risk factors for VRE colonization identified by multiple logistic regression analysis were hospital stay greater than 3 days prior to ICU admission (adjusted odds ratio [AOR], 3.6; 95% confidence interval [CI_{95}], 2.3 to 5.7), chronic dialysis (AOR, 2.4; CI_{95}, 1.2 to 4.5), and having been admitted to the study hospital one to two times (AOR, 2.3; CI_{95}, 1.4 to 3.8) or more than two times (AOR, 6.5; CI_{95}, 3.7 to 11.6) within the past 12 months. Of the 352 VRE-negative patients who had one or more follow-up cultures, 74 (21%) became VRE positive during their ICU stay (27 cases per 1,000 patient-ICU days).

CONCLUSION: The prevalence of VRE culture positivity on ICU admission was high and a sizable fraction of ICU patients became VRE positive during their ICU stay despite contact precautions for VRE-positive patients. This was likely due in large part to prior VRE exposures in the rest of the hospital where these control measures were not being used (*Infect Control Hosp Epidemiol* 2003;24:257-263).

Vancomycin-resistant *Enterococcus* (VRE) has become increasingly common among intensive care unit (ICU) patients. Data from the Intensive Care Antimicrobial Resistance Epidemiology project show that the prevalence of vancomycin resistance among clinical isolates of enterococci in the ICU setting was 10.4% in 1996.[1] However, the true prevalence of VRE colonization among ICU patients is higher. Previous studies, which used active surveillance rectal cultures, reported a VRE colonization rate between 6% and 20%[2-6] among patients admitted to the ICU and an incidence rate of becoming colonized with VRE during ICU admission of 10% to 14%.[4,6] Previous studies have also noted VRE colonization to be a significant risk factor for developing invasive infections with VRE among the critically ill,[5,6] for whom limited treatment options are available.

The Centers for Disease Control and Prevention released recommendations for preventing the spread of VRE within hospitals in 1995.[7] These recommendations included performing a culture survey of stools or rectal swabs, particularly in centers with many critically ill patients at high risk for VRE infection or colonization, along with instituting contact precautions for colonized patients. Despite these recommendations, the prevalence of VRE within U.S. hospitals continues to increase.[8] This has been attributed in part to incomplete implementation of the recommendations, along with a lack of active screening for VRE,[9] which is a labor- and resource-intensive process.[2,7]

Previous studies have shown that "colonization pressure" may promote VRE acquisition among critically ill patients.[10] Potentially, through the determination of easily identifiable risk factors for VRE colonization among newly admitted ICU patients, a strategy of selective active surveillance of high-risk patients may become a reasonable, cost-effective strategy for reducing colonization pressure within the ICU. A strategy of selective active surveillance for methicillin-resistant *Staphylococcus aureus*

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(MRSA) among high-risk patients has been shown to reduce the incidence of MRSA among ICU patients and to be cost-effective.[11,12]

The purposes of this study were to determine the prevalence of VRE colonization among patients admitted to an ICU and to define risk factors for colonization, which could potentially be used to develop a selective active surveillance program. In addition, we sought to determine the incidence of acquisition of VRE colonization among patients admitted to the unit.

METHODS

Barnes–Jewish Hospital is a 1,440-bed, urban, tertiary-care teaching hospital located in St. Louis, Missouri. A 19-bed medical intensive care unit (MICU) was chosen for the study. A rectal swab culture was performed on all patients admitted to the MICU between February 14 and December 31, 2000. If patients were admitted for more than 48 hours, additional rectal swab cultures were performed weekly and at the time of discharge from the MICU. In addition, all clinical cultures obtained from patients admitted for more than 48 hours were reviewed for the occurrence of VRE. Rectal swabs were inoculated onto bile-esculin azide agar with vancomycin at a concentration of 6 g/mL. These plates were incubated at 37°C and examined at 24, 48, and 72 hours. Growth on these plates was identified as VRE using a previously described phenotype-based scheme for the detection and characterization of VRE.[13] The infection control policy of the study unit was to place patients in contact isolation, using gowns and gloves, if they were known to be colonized with VRE prior to ICU admission or if they had a subsequent rectal or clinical culture positive for VRE.

Prospective data collection occurred for all patients admitted to the MICU for more than 48 hours. Data collected included demographics, medical history, admissions to Barnes–Jewish Hospital within the past 12 months, hospital and ICU admission dates, Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission, use of vascular access catheters, duration of mechanical ventilation, and the results of all clinical cultures. All in-hospital antimicrobial use prior to ICU admission was noted. For purposes of analysis, antimicrobials were divided into anti–gram-positive, anti–gram-negative, antianaerobic, and antifungal groups based on the reported antimicrobial spectrum of activity. Antimicrobial activity was expressed as categorical variables. Certain antimicrobials were classified into two or more groups (eg, imipenem was classified as having gram-negative, gram-positive, and anaerobic activity).

A VRE-prevalent case-patient was defined as a patient who either was admitted with known VRE colonization during the current hospitalization, or was found to have an admission rectal culture positive for VRE, or had VRE isolated from a clinical culture obtained within 48 hours of ICU admission. A VRE-incident case-patient was defined as a patient with a negative admission rectal culture and a subsequent (at least 48 hours after ICU admission) rectal or clinical culture positive for VRE. The incidence density for VRE acquisition was determined as the number of VRE incident cases per 1,000 patient-days at risk (ie, VRE-negative days).

Statistical analysis was performed using SPSS software (version 10.0 for Windows; SPSS, Inc., Chicago, IL). Comparisons of categorical variables were performed using the chi-square test or Fisher's exact test, where appropriate. Comparisons with continuous variables were performed using the Wilcoxon rank sum test. A P value of less than .05 on two-tailed testing was considered significant after the Bonferroni correction was applied to adjust for multiple comparisons on univariate testing. Multivariate analysis was performed using logistic regression. Variables were added to the model that were judged a priori to be clinically relevant to avoid spurious results with multiple comparisons.[14] Whereas pre-ICU antimicrobial use was considered for entry into the model for VRE colonization on admission, use of any class of antimicrobial was highly correlated with pre-ICU length of hospital stay. Also, when total days of antibiotic use prior to ICU admission was added to the model instead of pre-ICU length of hospital stay, the resulting model was overfitted (Hosmer and Lemeshow chi-square test, 12.7; $P = .047$), without a significant change in the adjusted odds ratio of the other predictor variables (data not shown). Therefore, pre-ICU length of stay was used in the final model. Multiple models were run, and the model with the highest log likelihood value was considered the best explanatory model. This study was approved by the Washington University Institutional Review Board and the need for written individual patient consent was waived.

RESULTS

During the study period, 530 patients were admitted to the MICU and stayed longer than 48 hours. Of these, 519 (98%) had an admission surveillance swab and were therefore eligible for study (Figure). The characteristics of the 519 study patients are listed in Table 1. The median age of this group was 61 years, and the mean admission APACHE II score was 23. Within this cohort, 127 (25%) of the patients were found to be colonized with VRE on admission. Of these patients, only 13 (10%) subsequently had VRE isolated in clinical cultures (1 wound and 12 urine specimens). The prevalence of VRE colonization did not change significantly during the study period (among the first third of patients admitted, 46 [27%] of 173 were colonized versus 44 [25%] of the second third and 37 [21%] of the final third; overall $P = .49$).

Risk factors associated with being colonized with VRE on ICU admission are listed in Table 2. After Bonferroni correction, a history of chronic renal failure requiring dialysis ($P < .001$), a pre-ICU length of hospital stay of 3 or more days ($P < .001$), one of more admissions to the study hospital within the 12 months before the current admission (relative risk of 2.2 for one to two admissions and 3.8 for more than two admissions), and the use of any antimicrobial prior to ICU admission were associ-

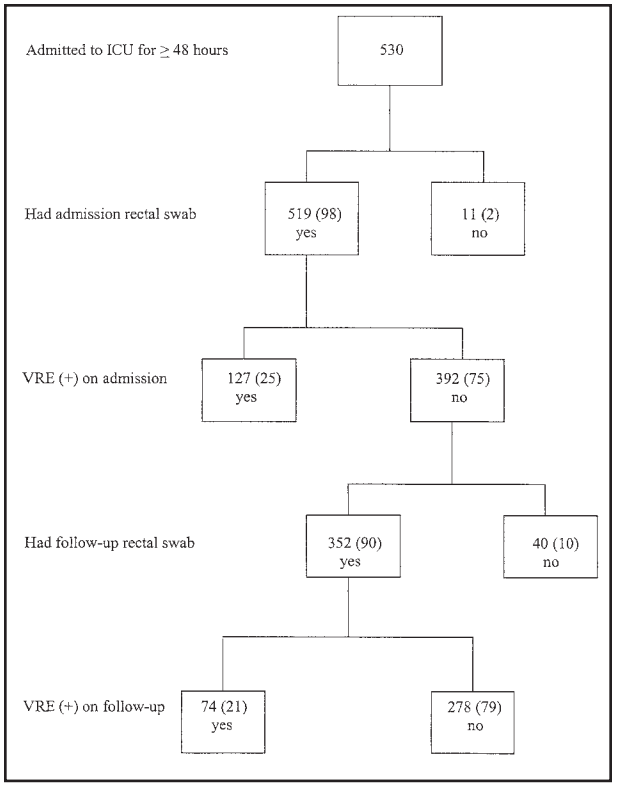

FIGURE. Distribution of the study population. Percentages are in parentheses. ICU = intensive care unit; VRE = vancomycin-resistant *Enterococcus*.

ated with VRE colonization at the time of ICU admission. The multivariate logistic regression analysis of factors associated with VRE colonization at the time of ICU admission is detailed in Table 2. Factors that were independently associated with VRE colonization at the time of ICU admission included having a pre-ICU length of hospital stay of 3 days or more (adjusted odds ratio [AOR], 3.6; 95% confidence interval [CI_{95}], 2.3 to 5.7], having a history of chronic renal failure requiring dialysis (AOR, 2.4; CI_{95}, 1.2 to 4.5), and having been admitted to Barnes–Jewish Hospital one to two times (AOR, 2.3; CI_{95}, 1.4 to 3.8) or more than two times (AOR, 6.5; CI_{95}, 3.7 to 11.6) within the past 12 months.

The predictive power of the model for risk factors for VRE colonization at the time of ICU admission is detailed in Table 3. The presence of at least one of the risk factors for VRE colonization at the time of ICU admission had a sensitivity of 94% and a specificity of 46%, and this was the case for 62% of the entire study population. In this cohort, having any one of these risk factors yielded a positive predictive value of 35% and a negative predictive value of 93%.

Three hundred fifty two (90%) of 392 study patients admitted to the ICU who had an initial negative rectal surveillance culture had one or more additional rectal cultures performed (median, 1; range, 1 to 14). Of these initially VRE-negative patients, 74 (21%) of 352 were subsequently found to be colonized with VRE. One patient had a positive urine culture for VRE 4 days after a negative admission rectal swab; the remaining cases were discovered by development of a positive rectal swab culture. The median time to development of a positive VRE culture

TABLE 1
DEMOGRAPHICS OF 519 PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT DURING THE STUDY PERIOD WITH AT LEAST ONE RECTAL SWAB CULTURE

Variable	No. (%)
Baseline patient characteristics	
Male	254 (49)
Mean age, y (median; range)	59 (61; 16–103)
White	282 (54)
CHF	104 (20)
COPD	131 (25)
Cancer	31 (6)
HIV infection	20 (4)
Diabetes mellitus	180 (35)
Baseline renal function	
Normal	395 (76)
Chronic renal failure	71 (14)
Chronic renal failure with dialysis	53 (10)
Cirrhosis	33 (6)
Bone marrow transplant	28 (5)
Surgery in past 28 days	18 (4)
Mean admission APACHE II score (range)	23 (5–47)
Pre-ICU antimicrobial use	
Anti–gram-negative	164 (31)
Anti–gram-positive	163 (31)
Antianaerobic	81 (15)
Antifungal	48 (9)
Processes of care	
Chemotherapy	11 (2)
Corticosteroid use	176 (34)
Tracheostomy	56 (11)
Antacid use	52 (10)
H_2 histamine antagonist	202 (39)
Sucralfate use	18 (4)
Vasopressor use	200 (39)
Enteral nutrition	233 (45)
Mechanical ventilation	342 (66)
Mean total CVC days (median)	5 (0)
⩾ 1 CVC inserted	244 (47)
Mean ventilator days (median)	6 (3)
Outcomes	
Clostridium difficile diarrhea	31 (6)
VRE prevalence	127 (25)
Mean pre-ICU LOS, d (range)	5 (1–91)
Mortality	135 (26)

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; ICU = intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation; CVC = central venous catheter; VRE = vancomycin-resistant *Enterococcus*; LOS = length of stay.

TABLE 2
COMPARISON OF PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT WHO WERE AND WERE NOT COLONIZED WITH VANCOMYCIN-RESISTANT *ENTEROCOCCUS*

Variable	No VRE (N = 392) No. (%)	VRE Positive (N = 127) No. (%)	*P*	AOR (CI_{95})‡
Mean age, y (range)	58 (16–103)	62 (21–102)	.03	
White	216 (55)	66 (52)	.73	
Male	192 (49)	62 (49)	.98	
CHF	80 (20)	24 (19)	.71	
COPD	97 (25)	34 (27)	.65	
Cancer	27 (7)	4 (3)	.12	
Chemotherapy	8 (2)	3 (2)	.74	
HIV infection	16 (4)	4 (3)	.79	
Diabetes mellitus	125 (32)	55 (43)	.02	
Baseline renal function				
Normal	315 (80)	80 (63)	Ref.	Ref.
Chronic renal failure	49 (13)	22 (17)	.05*	1.3 (0.7–2.3)
Chronic renal failure with dialysis	28 (7)	25 (20)	< .001*,†	2.4 (1.2–4.5)
Cirrhosis	24 (6)	9 (7)	.70	
Corticosteroid use	129 (33)	47 (37)	.40	
Enteral nutrition	163 (42)	62 (49)	.153	
Bone marrow transplantation	16 (4)	12 (9)	.02	
Surgery in past 28 days	12 (3)	6 (5)	.40	
Tracheostomy	35 (9)	21 (17)	.03	
Barnes–Jewish Hospital admissions in previous 12 mo				
None	247 (63)	42 (33)	Ref.	Ref.
1–2 admissions	102 (26)	41 (32)	.001*,†	2.3 (1.4–3.8)
> 2 admissions	43 (11)	44 (35)	< .001*,†	6.5 (3.7–11.6)
Pre-ICU hospital LOS ⩾ 3 d	96 (25)	65 (51)	< .001†	3.6 (2.3–5.7)
Mean APACHE II score	22	24	.03	
Pre-ICU antimicrobial use				
Anti–gram-negative	97 (25)	63 (50)	< .001†	
Anti–gram-positive	99 (25)	61 (48)	< .001†	
Antianaerobic	42 (11)	37 (29)	< .001†	
Antifungal	22 (6)	25 (20)	< .001†	

CHF = congestive heart failure; ICU = intensive care unit; APACHE = Acute Physiology and Chronic Health Evaluation; HIV = human immunodeficiency virus; COPD = chronic obstructive pulmonary disease; Ref. = reference group; LOS = length of stay; AOR = adjusted odds ratio; CI_{95} = 95% confidence interval; VRE = vancomycin-resistant *Enterococcus*.
*Obtained from univariate logistic regression.
†Significant after Bonferroni correction.
‡Other variables considered for inclusion in the final model: APACHE II score on admission, age, diabetes mellitus, bone marrow transplantation, pre-ICU antimicrobial use, and tracheostomy.

after ICU admission was 6 days (range, 2 to 36 days). Risk factors for VRE acquisition in the ICU are listed in Table 4. Increased mean APACHE II score on ICU admission (P = .002), sucralfate use (P = .003), vasopressor use (P = .01), tracheostomy in the ICU (P = .02), and *Clostridium difficile* diarrhea (P = .002) appeared to be associated with becoming VRE culture positive; however, none of these variables were significant after performing the Bonferroni correction for multiple comparisons. The overall incidence density of VRE acquisition was 27 cases per 1,000 patient-ICU days at risk. There was no significant increase in the incidence density between the initial third and the final two thirds of the study (data not shown).

DISCUSSION

This prospective cohort study of MICU patients found a high prevalence of VRE colonization among patients admitted to the ICU. Being a chronic dialysis patient, having been admitted to the study hospital within the 12 months prior to the current admission, and having stayed in the hospital for 3 days or more prior to the ICU admission were independently associated with being colonized with VRE on ICU admission. We also found a high rate of becoming VRE culture positive within the ICU despite the presence of an active surveillance culture program.

The finding of an increased prevalence of VRE colo-

nization among hemodialysis patients has been previously noted.[15,16] Our rate of colonization (20%) is much higher than those of these prior studies, which focused on outpatient hemodialysis subjects. We found that the risk of being colonized with VRE on admission to the ICU increased considerably when the patient had one or more hospitalizations at our facility within the past year, or if the patient had stayed in the hospital for 3 days or more prior to ICU admission. These findings suggest that a significant amount of nosocomial transmission of VRE may occur in our institution, both in and out of the ICU. Another potential explanation for this observation may be that patients who are frequently admitted to acute care facilities are also commonly admitted to skilled nursing facilities, which are known reservoirs of VRE.[17,18] We were unable to consistently ascertain whether patients in this study were transferred from a skilled nursing facility or another hospital. Previous individual exposure to antimicrobials, particularly vancomycin[19,20] and cephalosporins,[4,10] has been associated with having a positive VRE culture. However, a meta-analysis of antecedent vancomycin use and VRE colonization found no significant association in studies controlling for pre-ICU length of hospital stay.[21] Additionally, the use of antibiotics with anaerobic activity is associated with increased colony counts of VRE and environmental dissemination among VRE carriers.[22] Therefore, global antibiotic exposure, rather than individual antibiotic use, might be a better predictor of VRE prevalence and incidence within a given population. Because antibiotic use in this population was highly correlated with prolonged pre-ICU length of stay and problems with model overfitting when antibiotic days were used in the model, we chose to include the length of stay variable in our analyses.

Active surveillance cultures using rectal swab specimens were performed only in the study ICU at Barnes–Jewish Hospital. The policy for all other inpatient units was that all clinical stool specimens sent to the microbiology department for testing for *C. difficile* toxin were also tested for the presence of VRE. If this culture or other clinical specimens grew VRE, or if the patient was known to be colonized with VRE from a previous admission, then he or she was placed in contact isolation, using gowns and gloves. This testing strategy was similar to that being employed at another Midwestern hospital.[23] In that hospital, the strategy yielded comparable results: specifically, 14% of the patients were colonized with VRE on admission to the MICU and a pre-ICU length of hospital stay of 3 or more days was strongly associated with being VRE culture positive. That study, along with our results, suggests that active surveillance cultures and contact precautions for VRE in a single hospital unit can have only a limited impact on the prevalence of VRE in that unit, due to unrecognized transmission occurring elsewhere in the hospital where such control measures are not being used. Patients who became VRE culture positive did so roughly 1 week after ICU admission. This finding suggests that several patients had VRE fecal carriage at concentrations below the level of detection of the admission rectal swab culture, only to subsequently become positive for VRE after antibiotic exposure in the ICU resulted in an increase in enteric colony counts.

TABLE 3
SENSITIVITY AND SPECIFICITY OF A VARIABLE TO PREDICT VANCOMYCIN-RESISTANT *ENTEROCOCCUS* COLONIZATION AMONG ADMISSIONS TO THE INTENSIVE CARE UNIT

Variable	Sensitivity	Specificity	% of ICU Admissions
One predictor variable present			
A. Chronic renal failure with dialysis	22%	93%	10
B. Pre-ICU hospital LOS ⩾ 3 d	61%	76%	31
C. Barnes–Jewish Hospital admission in previous 12 mo	78%	63%	44
Two of three predictor variables present			
A and B	69%	66%	41
A and C	81%	59%	48
B and C	93%	48%	61
Any predictor variable present	94%	46%	62

ICU = intensive care unit; LOS = length of stay.

It is costly for institutions to perform active surveillance of all ICU admissions. An alternative method of screening would be to isolate and culture only patients who had one or more independent risk factors for VRE colonization. Previous studies have shown that selective surveillance for MRSA among high-risk patients reduces the transmission of that organism within an acute care setting[24,25] and is cost-effective.[11] In our study, a strategy to isolate and screen patients based on two readily available criteria (admission to our hospital within the past year and pre-ICU length of stay of 3 or more days during the current admission) would detect VRE colonization with a sensitivity of 93% and reduce the number of admission screening tests needed by 39%. The clinical effectiveness and cost-effectiveness of this approach for the control of VRE infection needs to be tested.

We found an extremely high rate of VRE acquisition among ICU patients (21%) and a relatively short median time to acquisition of VRE (6 days). These findings are similar to those from a study by Bonten et al.[10] in which 15% of MICU patients were colonized with VRE on admission and 29% of susceptible patients became colonized with VRE after a mean of 7.4 days. However, our acquisition rate was slightly higher than that obtained by Ostrowsky et al., who found an acquisition rate of 13% among surgical ICU patients.[4] The risk factors that were suggested on univariate analysis to be associated with

TABLE 4
UNIVARIATE ANALYSIS OF RISK FACTORS ASSOCIATED WITH ACQUISITION OF VANCOMYCIN-RESISTANT *ENTEROCOCCUS* DURING INTENSIVE CARE UNIT STAY

Variable	No VRE (N = 278) No. (%)	Acquired VRE (N = 74) No. (%)	*P*
Patient characteristics on admission			
Mean age, y (range)	58 (16–97)	58 (17–91)	.94
White	158 (57)	34 (46)	.10
Male	130 (47)	36 (49)	.77
CHF	58 (21)	13 (18)	.53
COPD	61 (22)	25 (34)	.04
Cancer	16 (6)	6 (8)	.43
Chemotherapy	7 (3)	1 (1)	1.0
HIV	8 (3)	6 (8)	.09
Diabetes	84 (30)	28 (38)	.21
Corticosteroids	89 (32)	30 (41)	.17
Enteral nutrition	121 (44)	37 (50)	.30
Cirrhosis	19 (7)	4 (5)	.80
Baseline renal function			
Normal	222 (80)	59 (80)	Ref.
Chronic renal failure	35 (13)	9 (12)	.93*
Chronic renal failure with dialysis	2 (8)	6 (8)	.88*
Bone marrow transplantation	12 (4)	4 (5)	.75
Surgery in past 28 days	9 (3)	1 (1)	.70
Mean APACHE II score (range)	22 (6–47)	25 (10–43)	.002
Processes of care			
Antacid use	29 (10)	9 (12)	.67
H_2 histamine antagonist	117 (42)	27 (37)	.38
Sucralfate use	6 (2)	7 (10)	.003
Vasopressor use	94 (34)	37 (50)	.01
⩾ 1 CVC inserted	126 (45)	42 (57)	.09
Mean total CVC days (range)	4 (0–43)	5 (0–24)	.65
Mechanical ventilation	183 (66)	57 (77)	.07
Re-intubation	32 (12)	12 (16)	.32
Tracheostomy > 48 h after ICU admittance	25 (9)	14 (19)	.02
Mean total ventilator days (range)	6 (0–52)	10 (0–69)	.04
ICU-related events			
Hepatic failure	53 (19)	12 (16)	.56
Acute respiratory failure	178 (64)	53 (72)	.22
Acute CHF	42 (15)	17 (23)	.12
Seizure or coma	18 (7)	2 (3)	.27
Clostridium difficile diarrhea	9 (3)	10 (14)	.002

VRE = vancomycin-resistant *Enterococcus*; ICU = intensive care unit; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; APACHE II = Acute Physiology and Chronic Health Evaluation; CVC = central venous catheter.
*Obtained from univariate logistic regression.

VRE acquisition include markers of increased severity of illness (ie, vasopressor use, high APACHE II score on admission, and tracheotomy), sucralfate use, and *C. difficile* diarrhea. *C. difficile* diarrhea has been associated with VRE acquisition in previous studies.[26] The higher severity of illness among colonized patients suggests that sicker patients who require increased contact with healthcare workers are at increased risk of acquiring VRE from the hands of healthcare workers. Observations of staff compliance with contact isolation procedures were not made during this study. However, a previous study in this unit found 78% compliance with glove use, but only 11% of the staff adequately washed their hands after leaving an isolated patient's room.[27] Because we could not record all antibiotic use during the ICU stay, this variable could not be analyzed as a potential risk factor for VRE acquisition.

Some limitations exist in our study. Because of limited resources, we could not include patients admitted for less than 48 hours in our study. These patients could have been an unrecognized reservoir for VRE transmission to other patients. Molecular typing of VRE isolates was not performed, so transmission patterns within the ICU could not be ascertained. We were also unable to collect daily data on VRE colonization pressure and antibiotic pressure, which have been noted to be associated with VRE transmission, during each individual ICU stay.[10]

Antimicrobial resistance is an increasing problem among critically ill patients. Resistance results in the use of more costly, broader-spectrum antimicrobials for empiric therapy in the ICU. Better understanding of the prevalence of colonization with resistant organisms among newly admitted ICU patients and the identification of risk factors for colonization in this patient population could allow for the development of new strategies for control. However, these new strategies would need to be tested to confirm both clinical effectiveness and cost-effectiveness.

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